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STERIC EFFECTS IN THE TRANSITION STATE OF TRANSANNULAR CYCLIZATION REACTIONS

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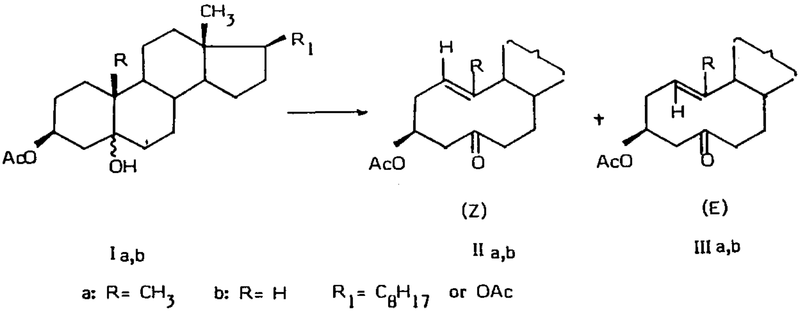
Abstract: Molecular mechanics calculations carried out on normal and 19-nor-5,10-seco-steroidal cyclodecenone systems, in order to explain regiochemistry and stereochemistry of transannular cyclization reactions of these molecules, suggest a good correlation with energies of model transition states.

Introduction

Considerable efforts have been made[1-7] to investigate conformational characteristics and structure-reactivity relationships in 5,10-seco-steroids (IIa,b and IIIa,b), obtained by oxidative fragmentation of the C(5)-C(10) bond of 5α - or 5β -hydroxy steroids (Ia,b Scheme 1). These results have shown that in the (E)-19-methyl series E-A is the only detectable ground state conformation in solution of IIIa (when R_1=OAc), and the major conformation of IIIa (when $R_1=C_8H_{17}$), which also exists in a minor conformation E-B (about 15%), while in the (E)-19-nor-5,10-secosteroid (IIIb, R_1=OAc) the major conformation of the ten-membered ring closely resembles the respective conformation of the corresponding 19-methyl containing analogues, E-A (Figure 1).[2,5]

Scheme 1



Under acid-catalyzed conditions the 19-methyl containing compounds (IIIa) readily undergo transannular cyclization by way of C(1)-C(5) bond formation to produce in the case of (IIIa, $R_1=C_8H_{17}$) two isomeric compounds[1] **1** and **2** in ca. 90% and 10% yield respectively (Scheme 2), and in the case of (IIIa, R_1=OAc) only one stereoisomer **3** in ca. 87% (Scheme 2) (all yields based on reacted substrate).

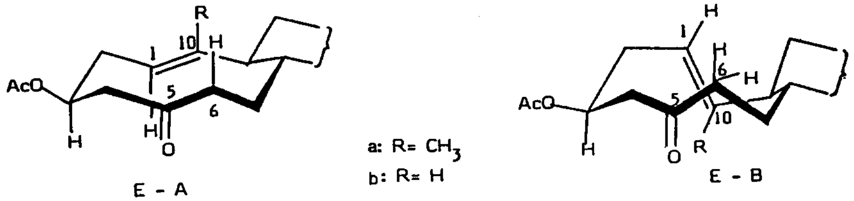
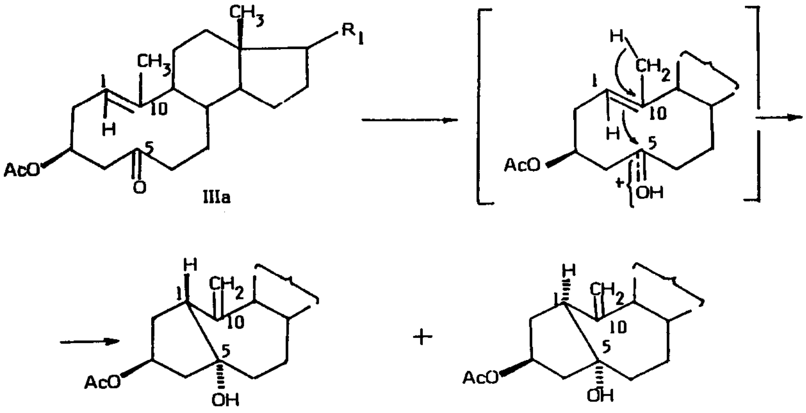


Figure 1. The two conformations of the ten-membered ring of IIIa,b

Scheme 2



1: 90% ($R_1=C_8H_{17}$)

3: 87% (R_1= OAc)

2: 10% ($R_1=C_8H_{17}$)

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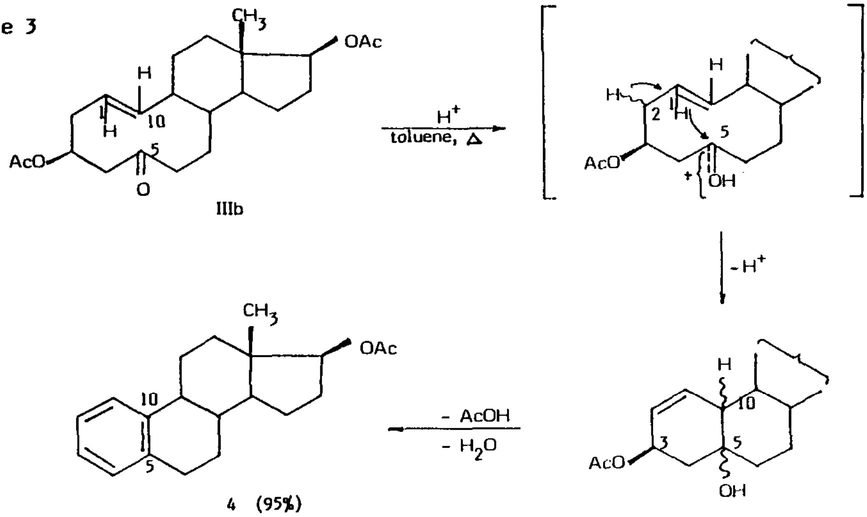
On the other hand, when a similar acid-catalyzed reaction was applied to the 19-nor compound (IIIb, R_1=OAc), it underwent cyclization (Scheme 3) by way of transannular C(5)-C(10) bond formation, accompanied by aromatization to the resulting ring A, to produce **4** in 95% yield (based on reacted substrate).

Examination of the thermal reactivity of (IIIa, $R_1=C_8H_{17}$), (IIIa, R_1=OAc) and (IIIb, R_1=OAc) shows that upon heating both IIIa compounds underwent cyclization to **1** (or **3**), while (IIIb, R_1=OAc) remained unchanged when subjected to similar conditions.

From these findings it follows that the transannular reactivity of the (E)-cyclodecenone system, incorporated in 5,10-seco-steroids of type IIIa,b, is highly influenced by the presence or the absence of the 19-methyl group. The 19-methyl group seems to be directing the regiospecificity of the transannular C-C bond formation in IIIa and IIIb (Schemes 2 and 3). Besides, it seems to be also influencing stereoselectivity of this reaction (Scheme 2), where IIIa ($R_1 = C_8H_{17}$) is capable of producing two stereoisomeric products (1 and 2), but 1 is formed preferentially, or exclusively.

Scheme 3



In this paper we describe the molecular mechanics calculations carried out to explain the stereochemistry of these reactions.

Results and Discussion

It is well known[10] that molecular mechanics may be used directly to predict the product ratios of chemical reactions under thermodynamic control, by computing heats of formation or strain energies of product compounds. For some kinetically controlled reactions the product ratio may be correlated[10] with the relative stabilities of the possible reaction products, assuming a late transition state. In this work we applied molecular mechanics calculations to the reactions of IIIa,b, represented on Schemes 2 and 3. The intention was to see whether the steric effects and particularely the effects of the 19-methyl group may explain the product distribution in these reactions (i) by assuming thermodynamic control of the reactions, and (ii) by carrying out calculations on the models of early transition states in the kinetically controlled reactions.

The molecular mechanics calculations have been performed using Allinger's MM2(82) program[8] with updated parameters[9] for ketones. In order to simplify the calculations, only partial structural models (Fig. 2) of the ground states and transition states of the molecules IIIa,b have been considered. Only one of the -OAc group rotamers (gauche) was taken into consideration in the calculations concerning the transition states. The three possible rotamers, considered in the ground state of the molecules, contribute about equally to the conformational energy difference between the two major conformations in solution E-A and E-B (Fig. 1).

Only the trans form of the ester group has been considered, since the cis form is more than 3 kcal/mol higher in energy.

The calculated conformational energy difference of a model (Fig. 2) of the 19-nor compound IIIb favors the conformation E-A for more than 2 kcal/mol (ΔE=2.6 kcal/mol), this being in agreement with the experimental finding that only conformation E-A exists in detectable amounts. When the 19-methyl group is introduced, the shape of the ring is changed in order to avoid 19-methyl...C(6)-hydrogen interactions. This change is accompanied by an increase of energy of the E-A conformation. A similar change in the conformation of the ten-membered ring occurs in the E-B conformation, as well, but the increase in energy is not so important. As a consequence, the energy difference between the E-B and E-A conformations is reduced (ΔE=0.6 kcal/mol) in the model of 19-methyl compound IIIa when compared to the 19-nor compound, and both conformations may be detected in solution.

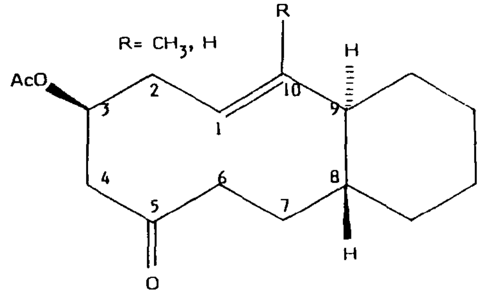


Figure 2. Partial structural model of the ground states of the molecules IIIa,b

When studying the reactivity of these compounds we assumed at first thermodynamic control of the reactions, and calculated and compared strain energies of the possible reaction products. The strain energies calculated for the possible products of the reactions presented in Schemes 2 and 3 are given in Fig. 3. Their values[*] indicate that the products with two fused six-membered rings are considerably more stable whether derived from IIIa or IIIb. The formation of **1**, **2** and **3** from IIIa (products containing fused five-membered and seven-membered ring) (Scheme 2) may be explained as being due to the potential tertiary carbo-cationic site C(10) in the transition state. However, calculated strain energies predict, as well that **2** should be a dominant product in the mixture of the two isomeric compounds **1** and **2**, contrary to what has been found experimentaly. The MM2 calculated conformational energies of the corresponding carbo-cationic C(10) intermediates differ for only 0.3 kcal/mol.

Therefore we conclude that the reaction is kinetically controlled and we apply molecular mechanics calculations to the model transition states ascribed to the reactions presented on Schemes 2 and 3.

Several assumptions are required in order to use molecular mechanics calculations to compute the steric energy of the model transition state (Fig. 4)[+]: (i) The steric energy of a model transition state is proportional to the height of the energy barrier of the cyclization reaction. (ii) The distance between C(1) and C(5) (or between C(5) and C(10)) varies as the

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[*] The 7-membered rings in **1** and **2** (obtained from IIIa) are in the most stable of the twist chair conformations, as determined earlier[3]. In the possible products of IIIb the cycloheptene ring is either chair (24.50 kcal/mol) or twist boat in the other isomer (23.28 kcal/mol).

[+] In Figures 4, 5 and 6, the full lines (—) denote C,C bonds and the broken lines (---) C,H bonds.

reaction proceeds and the partially formed bond length C(1)...C(5) (or C(5)...C(10)) may be regarded as a mean value[11] between the distance from C(1) to C(5) (or C(5) to C(10) in the starting molecule and in the final product. The atoms C(1) and C(5) (or C(5) and C(10)) have

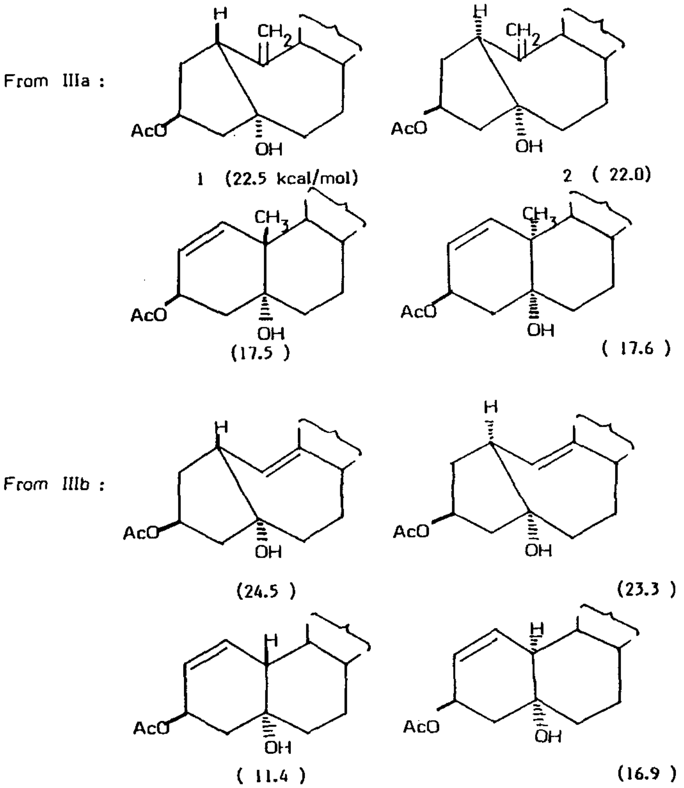

Figure 3. The possible reaction products and their calculated strain energies

therefore been fixed at the mean value distance. The remaining atoms were free of any restriction and their positions were changed in the course of the energy minimization. This model is justified by the fact that addition to a carbonyl group, for instance, is believed to be determined by steric approach control in nucleophilic additions of a large nucleophile[10], as well as in the case of a small nucleophile and sterically congested carbonyl compounds. (iii) The transition state energies were obtained when the steric energies associated with the close approach of C(1) and C(5) (or C(5) and C(10)) and with the streching of the C=C and C=O bonds, were substracted from the calculated steric energies of the model.

On the basis of these assumptions, molecular mechanics calculations were carried out to evaluate the energy values of the transition states derived from E-A and E-B conformations (Fig. 1). The calculated values of the energies and relative populations at 114°C are given in Table 1.

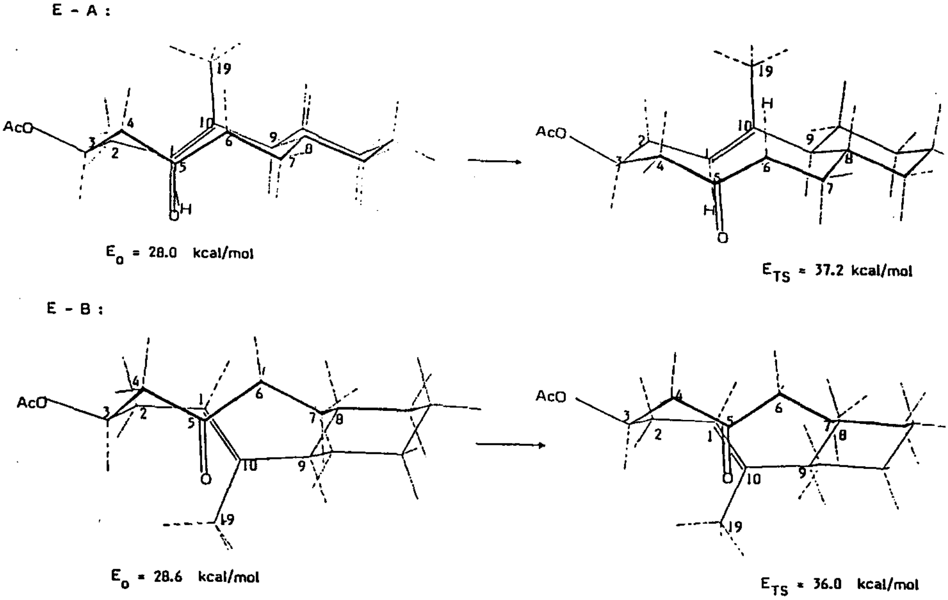

Figure 4. Energy-minimized (MM2) ground state and transition state geometries of the 19-methyl compounds and their calculated conformational energies

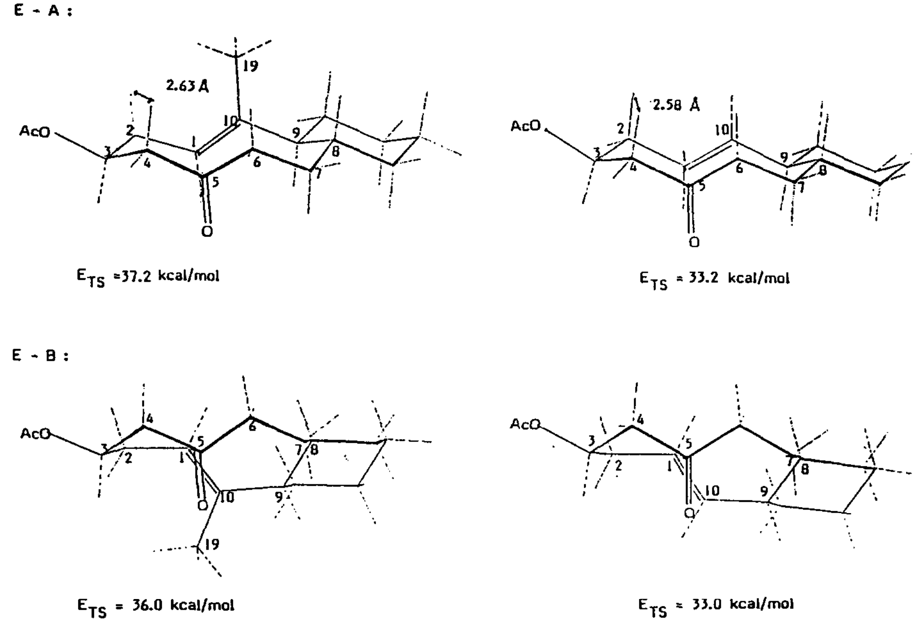

Figure 5. Energy-minimized (MM2) transition state geometries and the calculated conformational energies of the 19-methyl and 19-nor compounds

From these calculations it follows that the transannular reactivity of the (E)-cyclodecenone system incorporated in the modified seco-steroids of type III, is highly influenced by steric effects. Particularly important seems to be the presence or the absence of the 19-methyl group.

Table 1. Partial bond lengths ℓ (Å), relative transition state energies E (kcal/mol) and relative populations p (%) at 114°C

Series IIIa conformation	ℓ	E	p	**Series IIIb** conformation	ℓ	E	p
	(C1...C5)				(C1...C5)		
E-A	2.17	1.2	18	E-A	2.19	2.6	
E-B	2.19	0.0	82	E-B	2.23	2.3	
	(C5...C10)				(C5...C10)		
E-A	2.31	0.8		E-A	2.22	0.0	>92
E-B	2.29	5.0		E-B	2.21	6.3	

The experimentally obtained product distribution (90% of **1**, 10% of **2**) in the reaction presented in Scheme 2 is reproduced by calculations (82% of **1**, 18% of **2**)‡, because the transition state derived from the conformation E-A, which is directly related to product **2**, is 1.2 kcal/mol higher in energy than the transition state E-B leading to product **1**, (Fig. 4).

The analysis of the energy components in the E-A and E-B transition states reveals that the energy due to repulsion between the 19-methyl group and the 6β-hydrogen is not very big. However, the role of the methyl group is remarkable in determining the pathway of the energy minimization leading to the transition state in Fig.4 . Since the close approach of the 19-methyl and the 6β-hydrogen is unfavorable, in the E-A conformation, the shape of the ten-membered ring in the transition state is changed in order to relieve this repulsion. This change forces oxygen to approach C(1)-hydrogen, resulting in an important increase of energy of the E-A conformation. That the methyl group is responsible for this increase in energy can be seen when comparing transition state geometries of the 19-methyl and 19-nor compounds shown in Fig. 5. The distance between 2β- and 4β-hydrogens is larger in the 19-methyl than in the 19-nor compound (E-A conformation), thus reflecting the deformation of the ring which brings the C(1) -hydrogen and oxygen in close proximity. No such deformation exists in the corresponding conformation of the 19-nor compound and its energy is lower and almost equal to the energy of the transition state related to the E-B conformation.

The calculated transition state energy for the cyclization by way of C(5)...C(10) bond formation within the E-A conformation of the 19-methyl compound (Table 1), is lower than one would expect on the basis of the experimentally found product distribution. However, this is to be expected, since the MM2 method makes no allowance for the more favorable electronic change associated with the formation of tertiary carbo-cation produced in the cyclization with C(1)...C(5) bond formation.

The role of the methyl group is obvious when comparing the two series, IIIa and IIIb. The 19-nor compound does not give products by transannular C(1)...C(5) bond formations, but instead

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‡ Part of product **1** is probably formed experimentally by thermal cyclization[5,7].

forms thermodynamically more stable products with two fused six-membered rings. This is in agreement with the molecular mechanics calculations (Table 1), where both transition states leading to C(1)...C(5) bond formation (of nearly equal energies) are over 2 kcal/mol higher in energy than the transition state related to the E-A conformation, resulting in C(5)...C(10) bond formation. The lowest energy transition state calculated in the 19-nor series (Fig. 6) leads to product (C) which undergoes aromatization of the resulting ring A and produces **4**.

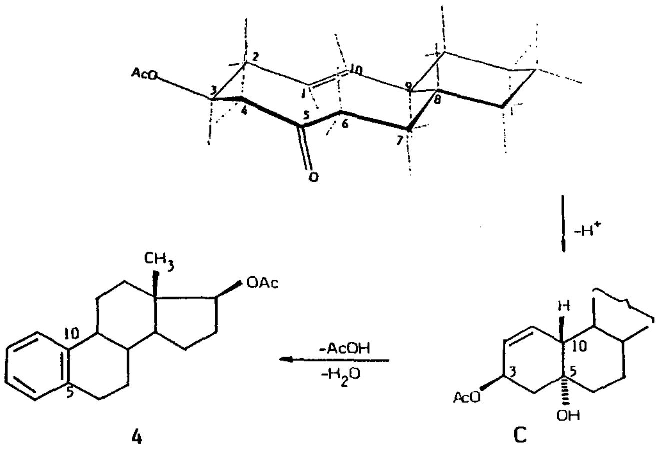

Figure 6. Energy-minimized (MM2) lowest energy transition state of the 19-nor compound, and the corresponding reaction product

Therefore, we conclude that the stereochemistry of these reactions is controlled by steric interactions in the transition state whose shape depends on the presence or the absence of the 19-methyl group.

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